DETAILED ACTION

1. This action is in response to papers filed 10/27/2011.

2. Claims 151-156 are pending.

3. The following rejections are reiterated. Response to arguments follows.

4. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 151-156 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 151-156 are indefinite over the phrase "preparing a RCG using at least one PCR primer wherein the RCG contains less than 1% (0.05%) of genomic material present in a whole genome:. It is unclear how the calculation of the genomic material present is determined because this percentage appears to be a function of the experimental conditions and hence the metes and bounds of the claims are not clear.

In particular the specification points to the fact that RCG may be derived using a DOP PCR with a primer having a Tag-Nx-Target motif wherein the target can include fewer or more than 7 nucleotides and X is an integer from 0 to 9 (p. 5 lines 10-25). The

specification further teaches that the RCG can include a plurality of fragments wherein 1% or 0.05% of the native genome is represented (p. 18 lines 12-20). The specification presents a specific probe (e.g. SEQ ID No. 4) with a 3' end of that is 8bp specific (p. 13 lines 22), however, the specification does not indicate which percentage of RCG will be obtained by using this sequence. Although the specification provides an example of a specific probe, the specification has not provided the calculation needed to determine which prepared RCGs would represent less than 1% or less than 0.05% percent of the genome. Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676 cited previously on the PTO-892) appears to indicate that an estimate of about one million DOP-PCR fragments generated from the entire human genome (p. 14676 2nd column 1st paragraph). Cheung et al. asserts that since the average size is 500 bp that there is a one in six change of being included in the DOP-PCR product. This appears to indicate that the RCG represented by the DOP-PCR used by Cheung is about 16% of the total genome. However, Cheung later states that if priming at the initial low temperature annealing is occurring because of all 6 specific base pairs on the 3' end, that there is an expectation to have amplified only about 1 of every 10 200 to 10000 bp (p 14678 2nd column last paragraph). Therefore if the entire human genome (3 X 10^9) is broken up into 200 bp fragments there were be 15,000,000 fragments. As such the DOP amplification would amplify 1500000 of these fragments (10%). This calculation is vastly different from the 16% initially discussed on p. 14676. Further, Cheung et al. indicates that the composition of the 3' fragment (e.g. the number of A, T, C, or Gs) would affect the determination because different bases have a different estimate of

occurrence (p. 14678 last paragraph), Further, Cheung points to the fact that subsequent PCR amplification at higher annealing temperatures makes use of the specificity at the 5' end and that Taq DNA polymerase is limiting (p. 14678 last paragraph to 14679 1st paragraph). As such it is unclear how to determine the RCG production based upon the guidance in Cheung as it appears that the composition of the 3' position, the annealing temperature, and Taq polymerase all are involved and as such it unclear what calculation is used to determine the percentage of RCG and therefore which randomly amplified primers would encompass the production of such a percentage.

Fisher et al. (Nucleic Acids Research 1996 Vol. 24 p. 4369) further illustrates the indefiniteness of the determination of the percent of RCG. Fisher et al. teaches that PCR conditions are crucial when using degenerate primers which anchors (p. 4369 last paragraph). Fisher et al. teaches that excessive stringency produces no amplicons whereas low stringency will permit slippage of the primer (p. 4369 last paragraph). As such Fisher et al. indicates that the amount of amplicons produces (e.g. the RCG) is in some way dependent upon the PCR amplification conditions. As such it is not clear if a DOP Primer used in one amplification constraint would produce the same percentage of RCG in another amplification constraint. As such it is not clear which primers would be encompassed in the limitation of preparing an RCG which contains less than 1% or less than 0.05% of the whole genome.

Even in post filing art there does not appear to be a particular calculation to determine which primers will produce RCGs containing less than 1% or 0.05% of the

whole genome. Osman et al. (Plant Physiology March 2003 Vol 131 p. 1294) a method of reducing complexity using DOP PCR primers similar to the ones described in the instant specification. Osman et al. teaches that the length of the specific sequence at the 3' end of the primer should decrease the complexity, but also reducing the annealing temperature will reduce the size of the PCR products (p. 1296 1st column last paragraph to 2nd column 1st paragraph). Table II indicates the total sequences amplified for each DOP primer with a unique 3' specific end. DOP Primer 2, 3, 4 are composed of different nucleotides but are all 11 mer in length. These primers produce a different total number of sequences (for example DOP 2 produced 25 sequences versus DOP 3 which produced 54 sequences). As such the post filing art indicates that it is not just the length of the DOP primer that is used to calculate the percentage of RCG, as Osman et al. shows that two DOP primers with the same 3' length will produce a different number of total sequences.

As such it appears that there are many components to determine the complexity reduction of a particular random primer. Not only does the length of the 3' specific region effect the percentage of RCG produce, but also the composition of the specific region (e.g. the number of bases that are A, G, C, and T), the amount of TAQ polymerase used in the reaction, and the annealing temperature. As such it is unclear the metes and bonds of the claims. In particular, as it is not clear how the percentage of RCG is calculated based upon the prior art disclosure and the specification, it is not clear which primers would produce the required percentage of genomic material. Rather, it is not clear is the RCG calculation is based upon some probably frequency

using the size of the specific section of the probe and the composition of the probe or an absolute calculation which further requires an analysis of the reaction constraints.

Response to Arguments

The reply traverses the rejection. A summary of the arguments set forth in the reply is provided below with response to arguments following.

It is acknowledged that the language used in the 112/2nd of "less than 1% (0.05%) of genomic material" is for brevity in the rejection and was intended to refer to both claims.

The reply asserts that the requirement of "less than 1% of genomic material present in a whole genome" is defined as the base of the percentage taken from the whole genome and that this number will not vary at all based on any particular set of experimental conditions (p. 3 last paragraph to p. 4 1st paragraph). The reply asserts that the percentage can be readily calculated mathematically and therefore there is no room for alterations caused by any particular set of experimental conditions (p. 4 1st paragraph). The reply asserts that so long as the RCG is prepared which contains less that 1% of the genomic material, any technique can be used (p. 4 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply asserts that the term RCG containing less than 1% of genomic material is fully defined as a specific percent of the whole genome. However, the 35 USC 112/2nd presented above is based upon the phrase " preparing a RCG using at least one PCR primer wherein the RCG contains less than 1% (0.05%) of genomic material present in a whole genome". Specifically although the ordinary artisan could after

performing the step determine rather or not the RCG is a particular percentage of total genomic material, the step of preparing such a randomly primed PCR derived RCG using a PCR primer is indefinite. In particular, as stated above, it is indefinite what is required in the preparing step of the claim. As the method requires "preparing a randomly primed PCR derived reduced complexity genome using at least one polymerase chain reaction primer" it is unclear the metes and bounds of this method step. In particular it is not clear which preparations would produce an RCG which contains less than 1% or 0.5% of genomic material present in a whole genome. The reply asserts that it doesn't matter what method is being used to produce a RCG which contains less than 1% or 0.5% of the genome. However, as discussed above, the resultant RCG is based upon many variables of the method used to prepare. Therefore the ordinary artisan could use, for example, the same primers but use different amounts of TAQ polymerase and produce different amounts of percentage of RCG. Therefore it is unclear which "preparing" steps would produce an RCG which contains less than 1% or 0.5% of the genomic material.

The reply presents an analysis of wood, asserting that although different techniques could be used that have varying degrees of accuracy the result is that the wood has a maximum length than any suitable technique may be used (p. 4 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

This analogy has been considered but the instant claims the issue which is indefinite is which "preparing" steps would produce an RCG which contains less than 1% or 0.5% of the genomic material. While it is acknowledge that one can measure RCG in a sample, it is unclear which preparations would produce such an RCG. As the claims are drawn to preparing a randomly primed PCR derived RCG using a primer, it is not clear which methods that teach such a preparation would produce an RCG which contains less than 1% of the genomic material and as such the metes and bounds of the claims are unclear.

The reply asserts that the portion of the specification identified only teaches that various RCGs can be prepared using various primers, but does not place any restrictions of the size of the RCG that is prepared (p. 5 1st 2 paragraphs). The reply asserts that the specification teaches various techniques for using a PCR primer to prepare an RCG and that the specification teaches that the length and complexity of an RCG that is prepared can be controlled by selecting DOP-PCR primers having shorter or longer Target and Nx nucleotides sequences (p. 5 last paragraph). The reply asserts that one of ordinary skill in the art would be able to routinely prepare RCGs using any PCR techniques, determine the length of the prepared RCGs, and compare the length to the whole genome to determine if the RCG prepared is less than 1% (or 0.05%) without undue experimentation (p. 5 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that the rejection points to the specification to note that the specification does not teach which preparations will produce an RCG that is less than 1% or 0.05%. The reply provides that the ordinary artisan would have to perform a step of determining the length of the prepared RCGs and compare the length to the whole genome to determine if the RCGs prepared are less length. However, this step is not in the claim. Rather, the claims are drawn to "preparing" a randomly primer PCR derived RCG using at least one primer. It is unclear which preparations would meet the metes and bounds of the claims, as it is not clear which preparing steps would produce such an RCG.

The reply asserts that the office is arguing that Cheung is inconsistent and that the applicants cannot vouch for its accuracy (p. 6 1st paragraph). The reply asserts that it is an oversimplification to conclude that 10% is vastly different from 16% based upon a rough calculation (p. 6 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The rejection set forth the issues in Cheung et al. to exemplify the differences in RCG products depending on the initial low temperature annealing conditions. As such Cheung et al. teaches that the sample preparation of PCR derived RCG with at least one primer would produce different RCGs representing different percentages of the whole genome. Although the calculations are rough, these calculations are merely provided to provide an example of using the same preparation with the same primer and producing different percents of genomic material.

The reply asserts that with regard to Fisher that the office has assumed without evidence that amplicons are equivalent to an RCG (p. 6 2nd paragraph). The reply asserts that although Fisher has demonstrated that variability may occur it is not seen how that variability renders the claim indefinite (p. 6 2nd paragraph). The reply asserts that one of ordinary skill in the art simply needs to measure the amount of RCG prepared and determines whether or not the amount is greater or less than 1% of the genomic material (p. 6 2nd paragraph). The reply asserts that the issue is not whether Osman's technique produces different amounts of PCR products using different primers but whether one of ordinary skill in the art would be able to determine rather the RCG prepared contains less or more than 1% of the genomic material (p. 6 2nd to last paragraph).

The reply asserts that it agrees that using different primers under varying experimental conditions can result in different amounts of RCG prepared, however, a person of ordinary skill in the art would need only to determine the amount of RCG present to determine whether the RCG contains more or less than 1% of the genomic material present in a whole genome (p. 6 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p 15 liens 23-25 of the instant specification). Further the specification describes RCGs as produced by PCR (p. 15 lines 30-31). As amplicons are reproducible fractions of an isolated genome

composed of a plurality of DNA fragments that can be produced by PCR, it is unclear the difference between amplicons and "randomly primed PCR derived RCG" as claimed. The variability discussed by Fisher renders that claim indefinite as it is not clear which preparations of the randomly primed PCR RCG using at least one primer will produce RCG which contain less than 1% or 0.05% of the genome. As such it is not clear which preparing randomly primed RCGs using a primer would encompass the same metes and bounds of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 151-153, 155-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Wei et al. (Somatic Cell and Molecular Genetics Vol. 20 1994 p. 401) and Saiki et al. (WO 89/11548 November 30, 1989) as evidenced by Von Eggeling (Cellular and Molecular Biology .1995 Vol. 41 p. 653).

It is noted that Shuber et al. and Saiki et al. have been previously cited on an IDS and are found in the prosecution history.

The following rejection is being made based upon the indefiniteness of the determination of the percentage of RCG. It appears that in the specification degenerated primers with at least 8 nucleotide specificity will produce RCG of less than 1% or 0.05%. As such the following combination of art teaches a degenerate based primer that has a specific segment of 16 nucleotides. As such based upon the indefiniteness of the claim, such a primer would be encompassed by the claims.

With regard to Claim 151-152, Shuber et al. teaches a method of detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (e.g. SNP) (column 5 lines 24-25). Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method in which human genomic DNA is fragmented by PCR amplification (column 2 lines 26-30 and column 4 lines 10-20). The instant

specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 15 lines 23-25 of instant specification). Further the instant specification describes RCGs as produced by PCR (p. 15 lines 30-31). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition provided. Therefore Shuber et al. teaches RCG that is PCR derived but does not teach that it is randomly prepared.

Shuber et al. teaches that ASO probes (e.g. allele specific oligonucleotides) are hybridized to RCGs (Figure 4 and column 6 lines 5-10). Shuber et al. teaches that the RCGs are immobilized to the solid support and the ASO probes are labeled. As such Shuber et al. teaches contacting a PCR derived RCG with SNP-ASOs. However, Shuber does not teach that the ASO probes are immobilized to the surface, but rather the RCGs are immobilized.

Shuber et al. teaches a method of determining rather the RCG is complementary to different mutant alleles comprised in the ASO probe by hybridization (column 6 lines 5-10 and figure 2A). Therefore Shuber teaches a method of hybridizing the RCG to the ASO to detect allelic differences.

Shuber et al. teaches that a plurality of RCGs from different patient samples can be compared and screened for particular mutations (Figure 4 and column 7 lines 50-60). The RCG in Shuber et al. is reproducible as the RCG is produced using a PCR methodology. As such depending on which RCG preparations are compared, these RCGs would have at least 50% of the same SNP-ASP sequences. Specifically if the RCG preparations are prepared so that the same genome is reproduced than the two

RCG preparations would be identical and as such include at least 50% of the same SNP-ASO sequences (e.g. 100% of the same SNP-ASO sequences).

The specification states if "a reproducible fraction is produced twice or more using the same experimental conditions the fractions produced in each repetition include at least 50% of the same sequences....For instance, if a RCG is produced by PCR another RCG can be generated under identical experimental conditions having at a minimum greater than 90% of the sequences in the first RCG". Shuber uses PCR technology to produce the RCG. As such under identical experimental conditions the amplicons made by the combination of art would be capable of producing a reproducible fraction of the genome and capable of being prepared to include at least 50% of the same SNP-ASO sequences if two or more RCG preparations are compared to one another.

In summary, Shuber et al. teaches preparing a PCR derived reduced complexity genome using at least one PCR primer, contacting the RCG with SNP-ASOs, wherein polymorphic loci corresponding to the SNP-ASOs are present with a frequency of at least 50% in a RCG and determining the presence or absence of the SNP allele. However, Shuber does not teaches that the RCG is randomly primed; that the RCG contains less than 20% of genomic material present in a whole genome, and that the SNP-ASOs are immobilized (rather in the case of Shuber the RCG is immobilized).

With regard to Claims 155-156, Shuber et al. teaches that the length of individual ASOs may be 16 to 25 nucleotides (column 4 lines 48-49).

Although Shuber et al. teaches a method of detecting ASOs in a sample, Shuber et al. does not teach that the sample is an RCG.

With regard to Claim 151-152, the art at the time of filing teaches production of RCGs. It appears that in the specification degenerated primers with at least 8 nucleotide specificity will produce RCG of less than 1% or 0.05%. Wei et al. teaches a degenerate based primer that has a specific segment of 16 nucleotides. Wei et al. teaches that a genomic sample was amplified using SIA PCR (p. 402 last full paragraph). Wei et al. teaches that this method uses two cycles in which the first cycle is a primer with 16 specific nucleotides at the 5' end and 6 degenerate nucleotides at the 3' end (p. 402 last paragraph). It appears that based upon the description in the specification and the lack of guidance to determine the calculation of RCG that having 16 specific nucleotides would produce a fragment of RCG that represents less than 0.05%. Wei et al. teaches that SIA derived DNA can be used to make region specific libraries for further analysis (p. 406 last paragraph). As such Wei With regard to Claims 151-152, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (abstract). Saiki et al. teaches that preparation of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detecting target nucleic acid sequences in test samples on demand (p. 9 lines 24-28).

With regard to Claim 53, Wei et al. teaches using SIA PCR, but does not specifically state that this is DOP PCR. However, as evidenced by Von Eggeling et al, SIA PCR is a nested DOP PCR system (p. 662 last paragraph).

The ordinary artisan would be motivated to modify the step of making the RCG taught by Shuber et al., because Wei et al. teaches that SIA derived DNA can be used to make region specific libraries for further analysis (p. 406 last paragraph). As such the method of Wei et al. would suggest a fractionalization of the genome to be used for further analysis of a reduced portion of the genome. Therefore the ordinary artisan would use the PCR methodology taught by Wei et al. to produce fractionalization of the genome to be used in the high throughput genomic mapping of the method of Shuber et al. to screen for specific ASO alleles in reduced complexity genomes of the whole population to screen for specific alleles which may be found anywhere in a given genome.

The ordinary artisan would have been motivated to modify the method of Shuber et al. to immobilize the ASO oligonucleotides to the solid support instead of the taught method of immobilizing the RCG to the solid support in order to prepare arrays separately and be able to test different samples quickly on premade arrays of probes. Saiki et al. teaches that preparation of immobilized probes can separate in time their sue, allowing for the support to be sued to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). As such the ordinary artisan would be motivated to prepare the solid supports ahead of time using the immobilization of the probe in order to produce a solid support which can be used on demand to rapidly detect SNPs in a target sequence.

Response to Arguments

The reply traverses the rejection. A summary of the arguments set forth in the reply is provided below with response to arguments following.

The reply asserts that the rejection was made based upon the indefiniteness of determining the percentage of RCG (p. 7 2nd paragraph). The reply asserts that the office has interpreted the teaching that a degenerate primer with at least 8 nucleotides specificity can be used to prepare an RCG of less than 1% or less than 0.05% (p. 7 2nd paragraph). The reply asserts that the specification does not inherently teach that a degenerate primer with at least 8 nucleotide specificity produces an RCG of less than 1% or less than 0.05 % (p. 7 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As noted in the 35 USC 112/2nd although the ordinary artisan can measure RCG based upon comparison to a whole genome, the step of preparing an RCG is indefinite. In particular it is unclear which primer assisted PCR will produce an RCG of less than 1% or less than 0.05%. The reply appears to be asserting that merely having at least 8 nucleotides will not specific produce an RCG of less than 1% or less than 0.05% and as such it is unclear which preparing steps will prepare an randomly primer PCR derived RCG using at least one primer. Wei et al. teaches a degenerate based primer that has a specific segment of 16 nucleotides. Wei et al. teaches that a genomic sample was amplified using SIA PCR (p. 402 last full paragraph). Wei et al. teaches that this method uses two cycles in which the first cycle is a primer with 16 specific nucleotides at the 5' end and 6 degenerate nucleotides at the 3' end (p. 402 last paragraph). It appears that based upon the description in the specification and the lack of guidance to

determine the calculation of RCG that having 16 specific nucleotides would produce a fragment of RCG that represents less than 0.05%. Wei et al. teaches that SIA derived DNA can be used to make region specific libraries for further analysis (p. 406 last paragraph). As such because Wei et al. teaches the step of preparing a randomly primed PCR derived RCG using at least one primer, Wei et al teaches the positive active step of the claimed method.

8. Claims 151-152, 154-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Guilfoye et al. (Nucleic Acids Research 1997 Vol. 25 p. 1854) and Saiki et al. (WO 89/11548 November 30, 1989).

It is noted that Shuber et al. and Saiki et al. have been previously cited on an IDS and are found in the prosecution history.

The following rejection is being made based upon the indefiniteness of the determination of the percentage of RCG. The specification teaches an adapter that has a 3 nucleotide overhang would yield a 64 fold reduction in complexity (p. 25 lines 2-15). As such a 6 nucleotide overhang would yield a 496 fold reduction in complexity (e.g. less than 0.05%).

With regard to Claim 151-152, Shuber et al. teaches a method of detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (e.g. SNP) (column 5 lines 24-25). Shuber et

al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method in which human genomic DNA is fragmented by PCR amplification (column 2 lines 26-30 and column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 15 lines 23-25 of instant specification). Further the instant specification describes RCGs as produced by PCR (p. 15 lines 30-31). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition provided. Therefore Shuber et al. teaches RCG that is PCR derived but does not teach that it is randomly prepared.

Shuber et al. teaches that ASO probes (e.g. allele specific oligonucleotides) are hybridized to RCGs (Figure 4 and column 6 lines 5-10). Shuber et al. teaches that the RCGs are immobilized to the solid support and the ASO probes are labeled. As such Shuber et al. teaches contacting a PCR derived RCG with SNP-ASOs. However, Shuber does not teach that the ASO probes are immobilized to the surface, but rather the RCGs are immobilized.

Shuber et al. teaches a method of determining rather the RCG is complementary to different mutant alleles comprised in the ASO probe by hybridization (column 6 lines 5-10 and figure 2A). Therefore Shuber teaches a method of hybridizing the RCG to the ASO to detect allelic differences.

Shuber et al. teaches that a plurality of RCGs from different patient samples can be compared and screened for particular mutations (Figure 4 and column 7 lines 50-60).

The RCG in Shuber et al. is reproducible as the RCG is produced using a PCR methodology. As such depending on which RCG preparations are compared, these RCGs would have at least 50% of the same SNP-ASP sequences. Specifically if the RCG preparations are prepared so that the same genome is reproduced than the two RCG preparations would be identical and as such include at least 50% of the same SNP-ASO sequences (e.g. 100% of the same SNP-ASO sequences).

The specification states if "a reproducible fraction is produced twice or more using the same experimental conditions the fractions produced in each repetition include at least 50% of the same sequences....For instance, if a RCG is produced by PCR another RCG can be generated under identical experimental conditions having at a minimum greater than 90% of the sequences in the first RCG". Shuber uses PCR technology to produce the RCG. As such under identical experimental conditions the amplicons made by the combination of art would be capable of producing a reproducible fraction of the genome and capable of being prepared to include at least 50% of the same SNP-ASO sequences if two or more RCG preparations are compared to one another.

In summary, Shuber et al. teaches preparing a PCR derived reduced complexity genome using at least one PCR primer, contacting the RCG with SNP-ASOs, wherein polymorphic loci corresponding to the SNP-ASOs are present with a frequency of at least 50% in a RCG and determining the presence or absence of the SNP allele. However, Shuber does not teaches that the RCG is randomly primed; that the RCG

contains less than 20% of genomic material present in a whole genome, and that the SNP-ASOs are immobilized (rather in the case of Shuber the RCG is immobilized).

With regard to Claims 155-156, Shuber et al. teaches that the length of individual ASOs may be 16 to 25 nucleotides (column 4 lines 48-49).

However, Shuber et al. does not teach the production of RCGs.

With regard to Claim 151-152, the art at the time of filing teaches production of RCGs by using ligation mediated PCR (e.g. adapter-PCR). With regard to Claims 151-152 and Claim 154, Guilfoyle et al teaches a ligation medicated PCR (e.g. adapter PCR) in which overhangs of different length (2-5 bases) and polarity are created (p. 1854 2nd column 1st paragraph and Figure 1). Guilfoyle et al. teaches that a 6 cutter enzyme would cleave a random sequence every 4096 bp and will produce on average 244 fragments (p. 1872 1st paragraph). As such a 6 nucleotide overhang would yield a 496 fold reduction in complexity (e.g. less than 0.05%). Guilfoyle et al. teaches that this reduction in complexity approach can be used as a library of complex genomes so that replication is avoided (p. 1873 last paragraph). As such Guilfoyle et al. teaches a method of reducing the complexity of the genome so that a library can be made which can be used for other screening methods.

The ordinary artisan would be motivated to modify the step of making the RCG taught by Shuber et al., because Guilfoyle et al. teaches that this reduction in complexity approach can be used as a library of complex genomes so that replication is avoided (p. 1873 last paragraph). As such the method of Guilfoyle et al. would suggest a fractionalization of the genome to be used for further analysis of a reduced portion of

the genome. Therefore the ordinary artisan would use the PCR methodology taught by Guilfoyle et al. to produce fractionalization of the genome to be used in the high throughput genomic mapping of the method of Shuber et al. to screen for specific ASO alleles in reduced complexity genomes of the whole population to screen for specific alleles which may be found anywhere in a given genome.

The ordinary artisan would have been motivated to modify the method of Shuber et al. to immobilize the ASO oligonucleotides to the solid support instead of the taught method of immobilizing the RCG to the solid support in order to prepare arrays separately and be able to test different samples quickly on premade arrays of probes. Saiki et al. teaches that preparation of immobilized probes can separate in time their sue, allowing for the support to be sued to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). As such the ordinary artisan would be motivated to prepare the solid supports ahead of time using the immobilization of the probe in order to produce a solid support which can be used on demand to rapidly detect SNPs in a target sequence.

Response to Arguments

The reply traverses the rejection. A summary of the arguments set forth in the reply is provided below with response to arguments following.

The reply asserts that for reasons cited above that there is no ambiguity in determining the amount of genomic material in an RCG and that the specification does not inherently teach a degenerate primer with at least 8 nucleotide specificity produces

an RCG of less than 1% or less than 0.05% the premise of the rejection is invalid (p. 7 last paragraph to p 8 1st paragraph).

This argument has been fully reviewed but has not been found persuasive.

These arguments have been fully reviewed but have not been found persuasive.

As noted in the 35 USC 112/2nd although the ordinary artisan can measure RCG based upon comparison to a whole genome, the step of preparing an RCG is indefinite. In particular it is unclear which primer assisted PCR will produce an RCG of less than 1% or less than 0.05%. The reply appears to be asserting that merely having at least 8 nucleotides will not specific produce an RCG of less than 1% or less than 0.05% and as such it is unclear which preparing steps will prepare an randomly primer PCR derived RCG using at least one primer. The specification teaches an adapter that has a 3 nucleotide overhang would yield a 64 fold reduction in complexity (p. 25 lines 2-15). As such a 6 nucleotide overhang would yield a 496 fold reduction in complexity (e.g. less than 0.05%). Guilfoyle et al teaches a ligation medicated PCR (e.g. adapter PCR) in which overhangs of different length (2-5 bases) and polarity are created (p. 1854 2nd column 1st paragraph and Figure 1). Guilfoyle et al. teaches that a 6 cutter enzyme would cleave a random sequence every 4096 bp and will produce on average 244 fragments (p. 1872 1st paragraph). As such a 6 nucleotide overhang would yield a 496 fold reduction in complexity (e.g. less than 0.05%). Guilfoyle et al. teaches that this reduction in complexity approach can be used as a library of complex genomes so that replication is avoided (p. 1873 last paragraph). As such Guilfoyle et al. teaches a method of reducing the complexity of the genome so that a library can be made which

can be used for other screening methods. Therefore Guilfoyle et al. teaches the positive active step of preparing a randomly primed PCR derived RCG using at least one primer.

Conclusion

1. No claims are allowed.

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Primary Examiner, Art Unit 1634